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Systematic organization of medicinal plant information: a monograph template proposal

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ABSTRACT

The use of medicinal plants in Brazil is widespread and is supported by public policies; it has the objective of providing the population with safe and effective herbal medicines of adequate quality. An action in these policies is to develop medicinal plant monographs to gather published information and decide which medicinal plants should be financed by the Brazilian government and distributed by the public health system. Currently, the monographs published worldwide do not present unified information regarding medicinal plants, and generally, they do not cover enough requirements for herbal medicine registration. The aim of this study is to develop a monograph model with standardized information not only about botany, agronomy, quality control, safety, and efficacy but also about relating regulatory aspects that support herbal medicine regulation. The development of standardized monographs favors the fast authorization and distribution of herbal medicines in the public system. The model also points out the lacking studies that should be carried out to supplement the necessary regulatory information of medicinal plants.

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Introduction

Brazil is one of the countries with the largest biodiversity of the world; however, most of it remains unexploited (Gonçalves et al., 2010). Brazil is also considered to house a large number of researchers. Nevertheless, knowledge generated by these studies is generally not applied for launching new products to the market, resulting in few herbal medicines made of Brazilian medicinal plants (Carvalho et al., 2008; SBPC, 2005).

In 2006, the Brazilian government published the National Policy of Integrative and Complementary Therapies, which includes phytotherapy in the public health system (Sistema Único de Saúde, SUS) (MS, 2006). In addition, in 2006, the National Policy of Medicinal Plants and Herbal medicines was published establishing the major actions to ensure the rational use of herbal medicines according to national legislation and international recommendations (Brasil, 2006).

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In 2009, the Brazilian Ministry of Health published the List of medicinal plants of interest for SUS (Rénisus), which included those considered as potentially valuable for the generation of herbal medicines. Researchers have been encouraged to make use of this list as a guide to select species to study. The resulting information regarding the species can then be used to prepare the national lists of herbal medicines and medicinal plants, and promote development and innovation in the field of medicinal plants (MS, 2009).

Several monographs have been published worldwide, some of which are used as sources of information by many countries, such as the WHO Monographs on Selected Medicinal Plants (Veiga Junior and Mello, 2008; WHO, 1999, 2003, 2004, 2007, 2009).

The two kinds of official monographs in Brazil are the Brazilian Pharmacopoeia, which includes quality control tests for synthetics and herbal medicines, and the *Formulário de Fitoterápicos da Farmacopoeia Brasileira*, which includes safety of herbal formulations for pharmaceutical compounding. Along with these official Brazilian references, some selected foreign pharmacopoeias are officially used in Brazil, such as the United States Pharmacopoeia (USP) and USP National Formulary, the International Pharmacopoeia (from the World Health Organization - WHO), and Germanic, Argentinean, British, European, French, Japanese, Mexican and Portuguese pharmacopoeias (Anvisa, 2009b), as well as other unofficial monographs: *Monografias de plantas medicinais brasileiras e aclimatadas* (Gilbert et al., 2005); *Farmácias Vivas* (Matos, 2000), and books including monographs of medicinal plants published for Brazilian phytotherapy public services. Scientific journals and articles are used also to gather information about medicinal plants. However, usually, each monograph or paper presents different approaches and do not face all the important requirements needed for a thorough documentation about medicinal plants, such as botanical authentication, cultivation, quality criteria, safety, efficacy, market, and regulatory issues (Veiga Junior and Mello, 2008).

Thus, a monograph template, including mandatory aspects as determined by Anvisa (Agência Nacional de Vigilância Sanitária) as well as international regulations, was developed. The objective is to systematize the available information on medicinal plants of interest to the Brazilian public health system.

The monograph template includes information considered relevant for the use of medicinal plants, based on a review of the scientific literature and databases to compile all previously published information on specific medicinal plants. This model's intent is to allow for remaining non-fulfilled items in the monograph be used to guide future research and financing by the Brazilian government.

Thus, after fulfilling this model with pre-published data on the plant species included in the Rénisus (Relação Nacional de Plantas Medicinais de Interesse ao SUS), it will be possible to identify which are the more studied medicinal plants having sufficient data on their safety and efficacy, to be subsequently financed by SUS, and gradually included in the list of herbal medicines with simplified registration by Anvisa (2008a). The products included in this list must follow a strict set of standardization so the registration process is easier and faster

than usual registration. For the less studied medicinal plants it would be possible to indicate which studies are needed to validate its use.

The monograph template presented herein is intended to be used by researchers funded by the Brazilian Ministry of Health to evaluate the plant species included in the Rénisus. Following their completion, monographs will be reviewed by experts in the areas of interest and will be initially published as a public consultation to allow all stakeholders to contribute to the final monograph. It is also envisaged that the monograph template will guide the research and inclusion of important information for the publication of medicinal plant data. Thus, articles and books published under this model may be quickly recognized by Anvisa, among their reference lists, for evidence of safety, efficacy, and quality of herbal medicines.

Material and methods

Building the template

To support the template proposal, a comparative and exploratory study was performed by a comparison and consideration of the set of information presented in the monographs listed by Anvisa Normative Instruction 05/10 (Anvisa, 2010e): WHO Monographs on selected medicinal plants, tomes 1-4 (WHO, 1999, 2004, 2007, 2009); European scientific cooperative on phytotherapy - Monographs on the medicinal uses of plant drugs (ESCOP, 1996); American Herbal Pharmacopoeia (Upton and Petrone, 1999); *Monografias de plantas medicinais brasileiras e aclimatadas* (Gilbert et al., 2005), British Herbal Compendium (Bradley, 2006); Expanded Commission E monographs (Blumenthal, 1999; Blumenthal et al., 2000); and *Vademécum nacional de plantas medicinales* (Cáceres, 2006). This data is available at Carvalho, 2011.

The next step was the evaluation of regulation requirements for herbal medicine registration and for plant notification at Anvisa, as well as requirements on regulations for herbal medicines from other agencies such as: European Medicines Agency (EMA), Health Canada (HC-SC), *Comisión Federal para la Protección contra Riesgos Sanitarios* (Cofepris), *Administración Nacional de Medicamentos, Alimentos y Tecnología Médica* (ANMAT), and the Paraguayan Health Ministry (Anmat, 1998, 1999a, b; Cofepris, 1998a, b, 2000, 2001, 2006, 2013; EMA, 2006a, b, c, d, 2007, 2008a, b, 2010a, b, c, d; HC-SC, 2003, 2006, 2007, 2010a, b; Paraguai, 1997). A preliminary template was created to verify if all the requirements were present, after which the template was submitted to peer review evaluation of the members of the Anvisa Herbal Medicine Technical Chamber (CATEF) and the Support Committee of Medicinal Plants and Herbal Medicines Policy from Brazilian Pharmacopoeia (CTT-APF) (Anvisa, 2010b; CATEF, 2010). The new template, with the reviewer-suggested modifications included, was tested at the preparation of the *Maytenus officinalis* Mabb., Celastraceae, monograph (unpublished results).

Results and discussion

The template

The proposed template is divided into seven main sections, namely: general information, pharmacognostic authentication, agronomical information, quality control, safety and efficacy, other information and references.

General information

This section must include all accepted names and basic information about the plant species, including vernacular name, scientific name, all known synonyms, images, and geographic distribution. Geographic distribution is important considering eventual financial support because Brazilian native species should be prioritized (Brasil, 2006).

Several useful free databases, such as “The plant list” and *Lista de espécies Flora do Brasil* can be accessed to ensure accuracy of the information. *Lista de espécies Flora do Brasil* database includes information on over 40,000 Brazilian species (JBRJ, 2012; MBG, 2013).

Pharmacognostic authentication

This section refers to plant parts or organs used as raw materials in herbal medicine production and should be as complete as possible to allow correct species identification. This information is usually found in pharmacopoeias. In Addition, *Brazilian Pharmacopoeia* presents figures showing the macro and microscopic characteristics from particularly useful herbal drugs (Anvisa, 2010a; Veiga Junior and Mello, 2008). Furthermore, this section should present information about all known species that could be used for counterfeit or misidentification, an important point for quality control. Data on other species used in folk medicine misidentified as the same plant or vernacularly named as the described plant species should be informed, particularly for native species. This information is valuable considering that in Brazil it is not rare that different species share the same vernacular name. Nevertheless, according to Brazilian regulation, to register a herbal medicine a complete dossier for the specific medicinal plant is mandatory, and all others species not presented at the dossier are considered as contamination (Anvisa, 2010a, b; Veiga Junior and Mello, 2008).

It is important to check for already collected and published data, which should also follow best practices, in this case, related to Botany. There are recommendations for collecting and cataloguing specimens, in relation to sustainability issues, as there are particular specifications for collecting, drying, and preparing of herbarium specimens (WHO/IUCN/WWF, 1993). Thus, if there is documentation regarding gathering and recording of vouchers specimens, this information should be included in the monograph.

Agronomical information

This section aids the implementation of the Good Agricultural Practices the first step in herbal medicine manufacture. This section should include data concerning the biology, phenology,

production system, cultivation method, processing, storage, and seed characteristics (Scheffer et al., 2006).

Furthermore, this section's data can help define strategies to improve the culture of target species to achieve better yields of selected phytopharmaceuticals. Agricultural practices can directly affect the quality of herbal medicines. International guidelines (e.g. WHO) can be used, given the lack of specific regulations in Brazil (Scheffer et al., 2006; WHO, 2003).

Agronomical information in this section enables the collection of data to assist projects for the standardized, homogeneous, and continuous production of plant materials; as well as the reproduction and genetic preservation of species of interest and biodiversity conservation. Information on the influence of seasonality over raw material productivity, active compound yield, and toxicity is important, as well as phytosociology, ecology, successional groups, and threat of extinction should be included.

Other crucial activities that should be controlled, such as soil analysis, pesticide contamination control, and water quality for irrigation to avoid plant drug pollution, should be described. Crop techniques and phytosanitary issues determine plant development and, consequently, the productivity and active compound yield (Scheffer et al., 2006; WHO, 2003). Much standardized agronomy information may not have yet been established for the medicinal plant described at the monograph, particularly when the plant is obtained by extractivism (wildcrafting). Thus, the item must be completed with the information “the requested data has not yet been published”.

Quality control

Concerning Brazilian regulation, the requirements for the quality control of herbal medicines are defined by RDC 14/10 (Anvisa, 2010e), and those related to pharmaceutical stability and analytical method validation are defined by RE 01/05 and 899/03 (Anvisa, 2003, 2005). For notifiable plants (herbal drugs traditionally chosen for simplified sales authorization), the quality control requirements are specified by RDC 10/10 (Anvisa, 2010c).

For herbal medicines, controls should be performed at all production steps, including the raw materials, which may be herbal drugs or herbal preparations, and the final product, the herbal medicine. All available published information on these tests and specifications standardized for the medicinal plant must be included in the monograph.

For the herbal drug, information about specifications on granulometry/particle size, organoleptic properties, presence of foreign materials such as ash, moisture, microscopic and macroscopic contaminants including fungi, bacteria, mycotoxins and heavy metals, should be given. Finally, qualitative and quantitative markers should be listed (Anvisa, 2010b).

For the herbal preparation, the extraction methods and the possibility of residual solvent presence must be included. For the final product, the control varies according to the dosage form, but it must guarantee the integrity and stability of the product, as well as the control level of microbial contamination (Anvisa, 2010d). Possible contaminants and the tests for identification and quantification of markers should be included

in the following three stages: herbal drug, herbal preparation, and the herbal medicine itself (Anvisa, 2010e).

In general, the official pharmacopoeias must be used to complete this section. The Brazilian Pharmacopoeia, 5th Ed. presents sixty monographs on medicinal plants and plant preparations. From these, only twelve refer to medicinal plants listed by Renisus. In the General Procedures section or in specific plant monographs of Brazilian Pharmacopoeia, protocols can be found for identification, microbiological control, ash content, humidity, and marker compound limits (Anvisa, 2010a).

Brazilian legislation prohibits the use of pesticides in medicinal plant crops. However, as this practice is allowed in several countries, and considering that Brazilian pharmaceutical companies can import the herbal raw materials, the presence of these substances must be stated. Therefore, all available information on pesticide limits for the medicinal plant should be included.

Any data available in the scientific literature regarding the best analytical techniques and specifications applied to each species, such as the use of thin-layer chromatography or high performance liquid chromatography for identification tests, should be stated.

Safety and efficacy

To register herbal medicines in Brazil, as done by the European community, pharmaceutical companies may present data on traditional use or non-clinical and clinical studies.

Information about traditional use

This section of the monograph should include information on the traditional use of the plant species, which, according to Brazilian law, must be demonstrated for a period of at least 20 years (long-term safe use), without serious adverse reports. Also, it should include studies demonstrating that the medicinal plant or herbal medicine does not contain toxic constituents.

Information about nonclinical and clinical assays

In agreement to Brazilian legislation, if there is not enough data on the traditional use of the medicinal plant, it is necessary to present data on non-clinical and clinical studies, which can be previously published. Only if enough data is not available, it will need to be tested by the company that intends to register the product. Considering this information, this section should include data on pharmacological and toxicological assays, separated by non-clinical and clinical studies (Anvisa, 2004, 2008b, 2010e; CNS, 1996, 1997). This structure was designed to present a panoramic view of the species and its derivatives, enabling detection of the most studied derivatives. However, many of the plants do not have complete clinical study data; subsequently, after reviewing the published literature and completing the monograph, it will be easy to find which species studies still require research and, thus, financing.

Data should be organized in a systematic way, such as by part of plant, derivative, chemical composition of the extract, tested doses, methodology, models, results, and references.

Non-clinical toxicology data should be divided into acute toxicity, sub-chronic, and chronic tests. According to Brazilian

RE 90/04, information regarding mutagenicity, genotoxicity, dermic sensibility, and cutaneous and ocular irritation should also be informed (Anvisa, 2004).

In accordance to RDC 47/09 or RDC 10/10, this section should also include information regarding route of administration, daily doses, posology, adverse effects, contraindications, risk groups, time limits for usage, precautions, interactions, and overdose effects (Anvisa, 2009a, 2010c).

Other information

Finally, the proposed template also presents a section on pharmaceutical form and formulation. Patent information can easily be found online at webpages such as *Instituto Nacional de Propriedade Industrial*, World International Property Organization, European Patent Office and Japan Patent Information Organization (EPO, 2011; INPI, 2011; JAPIO, 2011; WIPO, 2011). This information is important for the Ministry of Health, since it is preferable to finance research on non-patented extracts that can be produced at more affordable prices.

Other information should be included, if available in the scientific literature, such as special packaging, labeling, storage, and transportation (e.g., if the product must be protected from light). In addition, all known official or unofficial published monographs worldwide on the specific medicinal plant, including data regarding quality control, safety, and efficacy must be stated. Information about the regulatory conditions in other countries and licensing by Anvisa and/or other regulatory agencies, as obtained through official reports or publications, is also required. This information is important because this data shows that the medicinal plant has been evaluated and that its use in other countries was allowed, helping confirm its safety and effectiveness. Regulations of ANMAT, EMA, and HC-SC usually consider an existent herbal medicine register as a positive item in the registration process.

In Brazil, the extensive number of product registrations for the same species will favor its inclusion among those financed by SUS.

References

This section presents a Chart containing all scientific references used to elaborate the monograph on the medicinal plant used, including the category of the information (Pharmacology, Agronomy etc.).

The suggested referencing style is Vancouver. The scientific information required to complete the monograph can be found at PubMed, Lilacs, Napralert, Science Direct, CAPES thesis, Scifinder, Micromedex, Scopus, Biological Abstracts, Medscape, Toxnet, and other databases.

Conclusions

A review of published studies/information on each medicinal plant of interest to the Brazilian government according to the developed template should provide complete information on each medicinal plant. Information obtained in the monograph will help for the evaluation of available information on a specific plant species and the

necessary effort to complete any missing information. Such evaluation is important in the decision-making process for the funding of further studies on the quality, efficacy, and safety of medicinal plants. The scientific data on the monograph must be constantly re-evaluated and the monograph needs to be re-published, so that the new information available in the scientific literature can be updated. The suggested period for review of each monograph is each year, based on our experience with *M. ilicifolia* monograph (unpublished data): an evaluation showed that one year after the elaboration of the monograph, several scientific studies had already been published.

Authors' contributions

ACBC (PhD student) contributed in data collection about herbal medicines legislation and elaboration of the monograph template. LAS revised the international monographs and the monograph template. DS contributed to critical reading of the manuscript and supervised the elaboration of the monograph template. All the authors have read the final manuscript and approved the submission.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

- Anmat, 1998. Administración Nacional de Medicamentos, Alimentos y Tecnología Médica. Establécense normas reglamentarias que contemplen la importación, elaboración, fraccionamiento, depósito, comercialización y publicidad de drogas vegetales, medicamentos fitoterápicos y las personas físicas y jurídicas que intervengan en dichas actividades. in: Resolución 144 http://www.anmat.gov.ar/webanmat/mercotur/pdf_files/01ag_coprosal/AGREGADO_VII_Mercotur_Fitoterapicos.pdf, Accessed Dec 2010.
- Anmat, 1999a. Administración Nacional de Medicamentos, Alimentos y Tecnología Médica. Habilidadación establecimientos elaboradores, envasadores, fraccionadores e importadores de medicamentos fitoterápicos. in: Disposición 2671. http://www.anmat.gov.ar/webanmat/normativas_medicamentos_cuerpo.asp, Accessed Aug 2011.
- Anmat, 1999b. Administración Nacional de Medicamentos, Alimentos y Tecnología Médica. Solicitud de inscripción medicamentos fitoterápicos. in: Disposición 2673. http://www.anmat.gov.ar/webanmat/normativas_medicamentos_cuerpo.asp, Accessed in Dec 2010.
- Anvisa, 2003. Agência Nacional de Vigilância Sanitária. Determina a publicação do "Guia para validação de métodos analíticos e bioanalíticos". in: Resolução RE 899 on May 29, 2003. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES>, Accessed May 2013.
- Anvisa, 2004. Agência Nacional de Vigilância Sanitária. Dispõe sobre o "Guia para os estudos de toxicidade de medicamentos fitoterápicos". in: Resolução RE 90 on March 16, 2004. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES>, Accessed May 2013.
- Anvisa, 2005. Agência Nacional de Vigilância Sanitária. Autoriza ad referendum, a publicação do Guia para a Realização de Estudos de Estabilidade. in: Resolução RE 01 on July 19, 2005. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES>, Accessed May 2013.
- Anvisa, 2008a. Agência Nacional de Vigilância Sanitária. Determina a publicação da "Lista de medicamentos fitoterápicos de registro simplificado". in: IN 05 on December 11, 2008. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES>, Accessed May 2013.
- Anvisa, 2008b. Agência Nacional de Vigilância Sanitária. Aprova o regulamento para a realização de pesquisa clínica e dá outras providências. in: Resolução RDC 39 on June 05, 2008. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES>, Accessed May 2013.
- Anvisa, 2009a. Agência Nacional de Vigilância Sanitária. Estabelece regras para elaboração, harmonização, atualização, publicação e disponibilização de bulas de medicamentos para pacientes e para profissionais de saúde. in: RDC 47 on September 08 2009. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES>, Access May 2013.
- Anvisa, 2009b. Agência Nacional de Vigilância Sanitária. Trata da admissibilidade de Farmacopéias internacionais. in: RDC 37 on July 6, 2009. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES>, Accessed May 2013.
- Anvisa, 2010a. Agência Nacional de Vigilância Sanitária. Aprova a Farmacopeia Brasileira, 5ª edição e dá outras providências in: RDC 49 on November 23, 2010. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES>, Accessed May 2013.
- Anvisa, 2010b. Agência Nacional de Vigilância Sanitária. Comitê Técnicos Temáticos da Farmacopéia Brasileira. http://www.anvisa.gov.br/hotsite/farmacopeiabrasileira/conteudo/cont_comite_tecnico.htm, Accessed Oct 2010.
- Anvisa, 2010c. Agência Nacional de Vigilância Sanitária. Dispõe sobre a notificação de drogas vegetais junto à Agência Nacional de Vigilância Sanitária. in: RDC 10 de 10 de março de 2010. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/>

- ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES, Accessed May 2013.
- Anvisa, 2010d. Agência Nacional de Vigilância Sanitária. Dispõe sobre o registro de medicamentos fitoterápicos. in: RDC 14 March 30, 2010. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES>, Accessed May 2013.
- Anvisa, 2010e. Agência Nacional de Vigilância Sanitária. Lista de referências bibliográficas para avaliação de segurança e eficácia de medicamentos fitoterápicos. in: IN 05 on March 31, 2010. <http://portal.anvisa.gov.br/wps/wcm/connect/6805ba804f5ea576920df79a71dcc661/ConsolidadoVersaoIVpublicar.pdf?MOD=AJPERES>, Accessed May 2011.
- Blumenthal, M., 1999. The complete German commission E monographs. Therapeutic guide to herbal medicines. Integrative Medicine Communications, Boston.
- Blumenthal, M., Goldberg, A., Brinckmann, J., 2000. Herbal medicine: expanded Commission E monographs. Integrative Medicine Communications Newton.
- Bradley, P.R., 2006. British herbal compendium: a handbook of scientific information on widely used plant drugs. British Herbal Medicine Association, Exeter.
- Brasil, 2006. Aprova a Política Nacional de Plantas Medicinais e Fitoterápicos e dá outras providências. in: Decreto 5813 on June 22, 2006. http://www.planalto.gov.br/ccivil_03/_Ato2004-2006/2006/Decreto/D5813.htm, Accessed Jan 2014.
- Cáceres, A., 2006. Vademécum nacional de plantas medicinales. Editorial Universitaria, Universidad de San Carlos de Guatemala, Guatemala.
- Carvalho, A.C.B., 2011. Plantas medicinais e fitoterápicos: regulamentação sanitária e proposta de modelo de monografia para espécies vegetais oficializadas no Brasil, Programa de Pós-graduação em Ciências da Saúde. Universidade de Brasília, Brasília, p. 249.
- Carvalho, A.C.B., Balbino, E.E., Maciel, A., Perfeito, J.P.S. 2008. Situação do registro de medicamentos fitoterápicos no Brasil. Rev. Bras. Farmacogn. 18, 314-319.
- CATEF, 2010. Câmara técnica de medicamentos fitoterápicos. <https://www.anvisa.gov.br>, Accessed May 2011.
- CNS, 1996. Conselho Nacional de Saúde. Aprova as diretrizes e normas regulamentadoras de pesquisa envolvendo seres humanos. in: Resolução 196 on October 10, 1996. <http://www.bioetica.ufrgs.br/res19696.htm>, Accessed Jan 1996.
- CNS, 1997. Conselho Nacional de Saúde. Aprova normas de pesquisa envolvendo seres humanos para a área temática de pesquisa com novos fármacos, medicamentos, vacinas e testes diagnósticos. in: Resolução 251 on August 07, 1997. <http://www.huol.ufrn.br/doc/bioetica/41.pdf>, Accessed Jan 2014.
- Cofepris, 1998a. Comisión Federal para la Protección contra Riesgos Sanitarios. Buenas prácticas de fabricación para establecimientos de la industria químico farmacéutica dedicados a la fabricación de medicamentos. in: Norma Oficial Mexicana NOM-059-SSA1-1998 on October 04, 2000. <http://www.salud.gob.mx/unidades/cdi/nom/059ssa13.html>, Accessed Jan 2011.
- Cofepris, 1998b. Comisión Federal para la Protección contra Riesgos Sanitarios. Reglamento de insumos para la salud. <http://www.cofepris.gob.mx/MJ/Paginas/Normas-Oficiales-Mexicanas.aspx>, Accessed Nov 2009.
- Cofepris, 2000. Comisión Federal para la Protección contra Riesgos Sanitarios. Etiquetado de medicamentos. in: Norma Oficial Mexicana NOM-072-SSA1-1993. <http://www.salud.gob.mx/unidades/cdi/nom/072ssa13.html>, Accessed Jan 2011.
- Cofepris, 2001. Comisión Federal para la Protección contra Riesgos Sanitarios. Requisitos sanitarios que deben cumplir los fabricantes, distribuidores y proveedores de fármacos utilizados en la elaboración de medicamentos de uso humano. in: Norma Oficial Mexicana NOM-176-SSA1-1998. <http://www.salud.gob.mx/unidades/cdi/nom/176ssa18.html>, Accessed Jan 2011.
- Cofepris, 2006. Comisión Federal para la Protección contra Riesgos Sanitarios. Estabilidad de fármacos y medicamentos. in: Norma Oficial Mexicana NOM-073-SSA1-2005. <http://www.salud.gob.mx/unidades/cdi/nom/073ssa105.html>, Accessed Jan 2014.
- Cofepris, 2013. Comisión Federal para la Protección contra Riesgos Sanitarios. Buenas prácticas de fabricación para fármacos. in: Norma Oficial Mexicana NOM-164-SSA1-2013 on June 25 2013. <http://www.cofepris.gob.mx/MJ/Paginas/NormasPorTema/Buenas-practicas.aspx>, Accessed Jan 2014.
- EMA, 2006a. European Medicines Agency. Guideline on quality of herbal medicinal products/Traditional herbal medicinal products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003370.pdf, Accessed Jan 2011.
- EMA, 2006b. European Medicines Agency. Guideline on specifications: Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products /traditional herbal medicinal products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003393.pdf, Accessed Jan 2011.
- EMA, 2006c. European Medicines Agency. Reflection paper on the use of fumigants. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003352.pdf, Access in January 2011.
- EMA, 2006d. European Medicines Agency.Guideline on good agricultural and collection practice (GACP) for starting materials of herbal origin. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003362.pdf, Accessed Jun 2012.
- EMA, 2007. European Medicines AgencyGuideline on quality of combination herbal medicinal products/ traditional herbal medicinal products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003286.pdf, Accessed Jun 2012.
- EMA, 2008a. European Medicines Agency. Concept paper on the development of a guideline on a preparation of herbal teas. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003167.pdf, Accessed Jun 2012.
- EMA, 2008b. European Medicines Agency. Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003196.pdf, Accessed Jun 2012.
- EMA, 2010a. European Medicines Agency. Community herbal monograph. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001fa1d, Access in June 2012.

- EMA, 2010b. European Medicines Agency. Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003272.pdf, Accessed Jun 2012.
- EMA, 2010c. European Medicines Agency. Reflection paper on stability testing of herbal medicinal products and traditional herbal medicinal products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003370.pdf Accessed Jun 2012.
- EMA, 2010d. European Medicines Agency. Reflection paper on the level of purification of extracts to be considered as herbal preparations. http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500100375, Accessed Jun 2012.
- EPO, 2011. European Patent Office <http://www.epo.org/>, Accessed Jun 2012.
- ESCOP, 1996. European Scientific Cooperative on Phytotherapy. Monographs on the medicinal uses of plant drugs. Universidade de Exeter.
- Gilbert, B., Ferreira, J.L.P., Alvez, L., 2005. Monografias de plantas medicinais brasileiras e aclimatadas. ABIFISA, Curitiba.
- Gonçalves, A.E.S.S., Lajolo, F.M., Genovese, M.I., 2010. Chemical composition and antioxidant/antidiabetic potential of Brazilian native fruits and commercial frozen pulps. *J. Agric. Food Chem.* 58, 4666-4674.
- HC-SC, 2003. Health Canada. Natural health products regulations. <http://laws-lois.justice.gc.ca/eng/regulations/SOR-2003-196/>, Accessed Dec 2011.
- HC-SC, 2006. Health Canada. Evidence for safety and efficacy of finished natural health products. <http://www.hc-sc.gc.ca/dhp-mpps/prodnatur/legislation/acts-lois/prodnatur/index-eng.php>, Accessed May 2013.
- HC-SC, 2007. Health Canada. Evidence for quality of finished natural health products. <http://www.hc-sc.gc.ca/dhp-mpps/prodnatur/legislation/acts-lois/prodnatur/index-eng.php>, Accessed May 2013.
- HC-SC, 2010a. Health Canada. Natural health products ingredients database. <http://webprod.hc-sc.gc.ca/nhp-id-bdipsn/search-rechercheReq.do>, Accessed Jan 2014.
- HC-SC, 2010b. Health Canada. NHPD product monographs. <http://webprod.hc-sc.gc.ca/nhp-id-bdipsn/monosReq.do?lang=eng>, Accessed Jan 2014.
- INPI, 2011. Instituto Nacional de Propriedade Intelectual. pPI-Pesquisa em Propriedade Intelectual. <https://gru.inpi.gov.br/pPI/>, Accessed Jan 2014.
- JAPIO, 2011. Japan Patent Information Organization. <http://www.japio.or.jp/english/>, Accessed Jan 2014.
- JBRJ, 2012. Jardim Botânico do Rio de Janeiro. Lista de Espécies Flora do Brasil. <http://floradobrasil.jbrj.gov.br/jabot/listaBrasil/PrincipalUC/PrincipalUC.do?sessionId=F04FB957F65D2EB8E40DB1CB65C3F626>, Accessed May 2012.
- Matos, F.J.A., 2000. Plantas medicinais: guia de seleção e emprego de plantas usadas em fitoterapia no Nordeste do Brasil, 2 ed. Editora Universitária UFC, Fortaleza.
- MBG, 2013. Missouri Botanical Garden. The Plant List version 1.1. <http://www.theplantlist.org/>.
- MS, 2006. Política nacional de práticas integrativas e complementares no SUS. Atitude de ampliação de acesso. Ministério da Saúde. Brasília, DF, Brazil.
- MS, 2009. Relação de plantas medicinais de interesse ao SUS, Ministério da Saúde. <<http://portal.saude.gov.br/portal/arquivos/pdf/RENISUS.pdf>>, Accessed May 2012
- Paraguay, 1997. De productos para la salud y otros. in: Ley 1119/97. http://www.cej.org.py/games/Leyes_por_Materia_juridica/SALUD/LEY%201119.pdf, Accessed May 2012
- SBPC, 2005. Conclusões sobre o Simpósio "Plantas medicinais do Brasil: o pesquisador brasileiro consegue estudá-las? <http://www.jornaldaciencia.org.br/Detalhe.php?id=31331>, Accessed Jan 2014.
- Scheffer, M.C., Corrêa Júnior, C., Udry, M.C., Marques, N.E., Kornijezuk, R.M.P., 2006. Boas práticas agrícolas (BPA) de plantas medicinais, aromáticas e condimentares. Ministério da Agricultura, Pecuária e Abastecimento., Brasília.
- Upton, R., Petrone, C., 1999. *American herbal pharmacopoeia and therapeutic compendium*, Santa Cruz.
- Veiga Junior, V.F., Mello, J.C.P., 2008. As monografias sobre plantas medicinais. *Rev. Bras. Farmacogn.* 18, 464-471.
- WHO, 1999. Monographs on selected medicinal plants. World Health Organization, Geneva.
- WHO, 2003. Guidelines on good agricultural and collection practices (GACP) for medicinal plants. World Health Organization, Geneva.
- WHO, 2004. Monographs on selected medicinal plants. World Health Organization, Geneva.
- WHO, 2007. Monographs on selected medicinal plants. World Health Organization, Geneva.
- WHO, 2009. monographs on selected medicinal plants. World Health Organization, Geneva.
- WHO/IUCN/WWF, 1993. World Health Organization/ The International Union for Conservation of Nature and Natural Resources/ World Wide Fund for Nature. Guidelines on the conservation of medicinal plants, Gland.
- WIPO, 2011. United Nations. World international property organization. <http://www.wipo.int/portal/index.html.en>, January 2014.

Monograph template:

1. General information

- 1.1. Latin name
- 1.2. Synonyms
- 1.3. Family
- 1.4. Image of the plant
- 1.5. Popular names
- 1.6. Geographical distribution

2. Botanical authentication

- 2.1. Part used/organ types
- 2.2. Macroscopic description
- 2.3. Microscopic description
- 2.4. Information on similar plant species that can be used as adulterants
- 2.5. Information on voucher specimens

3. Agronomic information

- 3.1 Biology and phenology
 - 3.1.1. Sexual system
 - 3.1.2. Flowering time
 - 3.1.3. Fruiting period
- 3.2. Form of fruit and seed dispersal
- 3.3. Production system
 - 3.3.1. Information on seeds
 - 3.3.2. Harvesting and processing
 - 3.3.3. Seed weight (by mg/1,000 seeds)
 - 3.3.4. Productivity
 - 3.3.5. Dormancy of seeds
 - 3.3.6. Longevity and storage
- 3.4. Germination
 - 3.4.1. Information on crop
 - 3.4.2. Description
 - 3.4.3. Propagation
 - 3.4.4. Growth and production
 - 3.4.5. Characteristics of the soil
 - 3.4.6. Climatic characteristics
 - 3.4.7. Time of collection/harvesting
 - 3.4.8. Habit and regeneration
 - 3.4.9. Consortium
 - 3.4.10. Agroforestry system
 - 3.4.11. Breeding
 - 3.4.12. Pests and diseases (occurrence, level of damage and control)
- 3.5. Processing information
 - 3.5.1. Drying
 - 3.5.2. Processing
 - 3.5.3. Expected return
 - 3.5.4. Packing
- 3.6. Storage information
- 3.7. Information on seasonal variation of markers
- 3.8. Information about whether the management affects markers
- 3.9. Ecological aspects

4. Quality control information (to be completed for plant species, plant preparations, and the final product - the herbal medicine).

Chart 1: Information about quality control

| Herbal drug | Herbal preparation | Herbal medicine |
|--|------------------------|---|
| Granulometry/ particle size | Description | Dosage forms |
| - | Methods of production | Specific tests for each pharmaceutical form |
| - | Physicochemical tests | - |
| Organoleptic characteristics | | - |
| Purity requirements | | |
| | Microbiological testes | |
| | Humidity | |
| | Heavy metals | |
| | Chemical residues | |
| | Ashes | |
| Phytochemical analysis | | |
| Identification test | | |
| Quantification tests (Chemical constituents and concentrations): | | |
| Described | | |
| Markers or active compounds | | |
| Other considerations related to quality control | | |

5. Safety and efficacy information

- 5.1. Information on traditional use
- 5.2. Information about nonclinical and clinical assays
 - 5.2.1. Nonclinical toxicology
 - 5.2.1.1. Subchronic
 - 5.2.1.2. Chronic
 - 5.2.1.3. Genotoxicity
 - 5.2.1.4. Dermic sensibilization
 - 5.2.1.5. Cutaneous irritancy
 - 5.2.1.6. Ophthalmic irritancy
 - 5.2.2. Nonclinical pharmacology
 - 5.2.2.1. Nonclinical pharmacological assays
 - 5.2.3. Clinical trials
 - 5.2.3.1. Phase I
 - 5.2.3.2. Phase II, including pharmacokinetics and pharmacodynamics
 - 5.2.3.3. Phase III
 - 5.2.3.4. Phase IV
- 5.3. Summary of actions and indications for drugs derivatives
- 5.4. Routes of administration
- 5.5. Daily dose
- 5.6. Posology
- 5.7. Period of use
- 5.8. Contraindications
- 5.9. Risk groups
- 5.10. Warnings
- 5.11. Adverse effects
- 5.12. Drug interactions
 - 5.12.1. Described
 - 5.12.2. Potential
- 5.13. Overdose information
 - 5.13.1. Description of the clinical situation
 - 5.13.2. Actions to be taken

6. Other information

- 6.1. Dosage forms/formulations described in the literature
- 6.2. Products registered at Anvisa and other regulatory agencies
- 6.3. Packaging and labeling information
- 6.4. Monographs about the medicinal plant in oficial and unofficial compendia/codex
- 6.5. Patents applied for the plant species
- 6.6. Curiosities

7. List of references**Chart 2: References**

| No | Author and title | Year | Knowledge area | Reference |
|----|------------------|------|----------------|-----------|
|----|------------------|------|----------------|-----------|